Medical Policy
Preimplantation Genetic Testing

Table of Contents
• Policy: Commercial
• Policy: Medicare
• Authorization Information
• Coding Information
• Description
• Information Pertaining to All Policies
• Policy History
• References

Policy Number: 088
BCBSA Reference Number: 4.02.05
NCD/LCD: N/A

Related Policies
Infertility Diagnosis and Treatment, #086

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Preimplantation genetic testing for monogenic/single gene diseases (PGT-M)
Preimplantation genetic testing for monogenic/single gene defects (PGT-M) may be MEDICALLY NECESSARY including IVF with or without ICSI, even if the member is not infertile, when ALL of the following criteria are met:

1. The member/couple has undergone genetic counseling, AND
2. The member has a > 5% chance of live birth per cycle of IVF with or without ICSI, AND
3. PGT-M is for evaluation of an embryo at an identified elevated risk for one of the following:
   a. A genetic disorder that is associated with severe disability or has a lethal natural history, such as when:
      i. Both partners are known carriers of a single gene autosomal recessive disorder,
      ii. One partner is a known carrier of a single gene autosomal recessive disorder and the partners have one offspring that has been diagnosed with that recessive disorder,
      iii. One partner is a known carrier of a single gene autosomal dominant disorder, or
      iv. One partner is a known carrier of a single X-linked disorder.
   b. A structural chromosomal abnormality such as for a parent with balanced or unbalanced chromosomal translocation.

Preimplantation genetic testing for monogenic/single gene diseases (PGT-M) in conjunction with IVF is INVESTIGATIONAL in patients/couples who are undergoing IVF in all situations other than those specified above.

Examples of MEDICALLY NECESSARY diagnoses include but are not limited to the following:
Preimplantation genetic testing for monogenic/single gene diseases (PGT-M) in conjunction with in vitro fertilization (IVF) in couples not known to be infertile may be considered MEDICALLY NECESSARY when used to evaluate human leukocyte antigen (HLA) status alone in families with a child with a bone marrow disorder requiring a stem cell transplant, and in whom there is no other source of a compatible bone marrow donor other than an HLA matched sibling.

Preimplantation genetic testing for a chromosomal rearrangements or size of the chromosome (PGT-SR) abnormality may be MEDICALLY NECESSARY including IVF with or without ICSI, even if the member is not infertile, when ALL of the following criteria are met:

1. The member/couple has undergone genetic counseling, AND
2. The member has a > 5% chance of live birth per cycle of IVF with or without ICSI, AND
3. Is for the evaluation of an embryo at an identified elevated risk of being affected by a genetic disorder involving the rearrangement or size of a chromosome, i. such as for a parent with a balanced or unbalanced chromosomal translocation.

Preimplantation genetic testing for aneuploidies (PGT-A)
Preimplantation genetic testing for aneuploidies (PGT-A)/the correct number and size of all chromosomes in an embryo in conjunction with IVF with or without ICSI is INVESTIGATIONAL in patients/couples who are undergoing IVF in all situations.

Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
- For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Prior authorization is required.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>Prior authorization is required.</td>
</tr>
</tbody>
</table>
CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>89290</td>
<td>Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos</td>
</tr>
<tr>
<td>89291</td>
<td>Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos</td>
</tr>
</tbody>
</table>

Description

PREIMPLANTATION GENETIC TESTING

Preimplantation genetic testing describes various adjuncts to an assisted reproductive procedure (see MP 086, Assisted Reproductive Services Infertility Services) in which embryonic DNA is sampled and genetically analyzed, thus permitting deselection of embryos harboring a genetic defect before implantation of an embryo into the uterus. The ability to identify preimplantation embryos with genetic defects before implantation provides an alternative to amniocentesis, chorionic villus sampling, and selective pregnancy termination of affected fetuses. Preimplantation genetic testing is generally categorized as either diagnostic preimplantation genetic testing for monogenic/single gene diseases (PGT-M) (formerly known as preimplantation genetic diagnosis [PGD]) or testing for aneuploidies (PGT-A) (formerly known as preimplantation genetic screening [PGS]). PGT-M is used to detect genetic evidence of a specific inherited disorder, in the oocyte or embryo, derived from mother or couple, respectively that has a high risk of transmission. PGT-A is not used to detect a specific abnormality but instead uses similar techniques to identify the number of chromosomes and their size in an embryo in the absence of a known heritable disorder. This terminology, however, is not used consistently (eg, some authors use PGD when testing for a number of possible abnormalities in the absence of a known disorder).

Biopsy

Biopsy for PGT-M can take place at 3 stages: the oocyte, cleavage stage embryo, or the blastocyst. In the earliest stage, both the first and second polar bodies are extruded from the oocyte as it completes the meiotic division after ovulation (first polar body) and fertilization (second polar body). This strategy thus focuses on maternal chromosomal abnormalities. If the mother is a known carrier of a genetic defect and genetic analysis of the polar body is normal, then it is assumed that the genetic defect was transferred to the oocyte during meiosis.

Biopsy of cleavage stage embryos or blastocysts can detect genetic abnormalities arising from either the maternal or paternal genetic material. Cleavage stage biopsy takes place after the first few cleavage divisions when the embryo is composed of 6 to 8 cells (ie, blastomeres). Sampling involves aspiration of one and sometimes 2 blastomeres from the embryo. Analysis of 2 cells may improve diagnosis but may also affect the implantation of the embryo. In addition, a potential disadvantage of testing at this phase is
that mosaicism might be present. Mosaicism refers to genetic differences among the cells of the embryo that could result in an incorrect interpretation if the chromosomes of only a single cell are examined. The third option is sampling the embryo at the blastocyst stage when there are about 100 cells. Blastocysts form 5 to 6 days after insemination. Three to 10 trophectoderm cells (outer layer of the blastocyst) are sampled. A disadvantage is that not all embryos develop to the blastocyst phase in vitro and, when they do, there is a short time before embryo transfer needs to take place. Blastocyst biopsy has been combined with embryonic vitrification to allow time for test results to be obtained before the embryo is transferred.

Analysis and Testing

The biopsied material can be analyzed in a variety of ways. Polymerase chain reaction or other amplification techniques can be used to amplify the harvested DNA with subsequent analysis for single genetic defects. This technique is most commonly used when the embryo is at risk for a specific genetic disorder such as Tay-Sachs disease or cystic fibrosis. Fluorescent in situ hybridization (FISH) is a technique that allows direct visualization of specific (but not all) chromosomes to determine the number or absence of chromosomes. This technique is most commonly used to screen for aneuploidy, sex determination, or to identify chromosomal translocations. FISH cannot be used to diagnose single genetic defect disorders. However, molecular techniques can be applied with FISH (eg, microdeletions, duplications) and, thus, single-gene defects can be recognized with this technique. Performing PGT-A using FISH is known as PGT-A version 1.

Another more recent approach is array comparative genome hybridization testing at either the 8-cell or, more often, the blastocyst stage, also known as PGT-A version 2. Unlike FISH analysis, hybridization allows for 24 chromosome aneuploidy screening, as well as more detailed screening for unbalanced translocations and inversions and other types of abnormal gains and losses of chromosomal material. Other PGT-A version 2 methods include single nucleotide variant microarrays and quantitative polymerase chain reaction.\textsuperscript{1,2} Next-generation sequencing such as massively parallel signature sequencing has potential applications to prenatal genetic testing and is grouped with PGT-A version 2 techniques in some literature and referred to as PGT-A version 3 in other literature.

Embryo Classification

Three general categories of embryos have undergone preimplantation genetic testing, which are discussed in the following subsections.

**Embryos at Risk for a Specific Inherited Single-Gene Defect**

Inherited single-gene defects fall into 3 general categories: autosomal recessive, autosomal dominant, and X-linked. When either the mother or father is a known carrier of a genetic defect, embryos can undergo PGT-M to deselect embryos harboring the defective gene. Sex selection of a female embryo is another strategy when the mother is a known carrier of an X-linked disorder for which there is no specific molecular diagnosis. The most common example is female carriers of fragile X syndrome. In this scenario, PGT-M is used to deselect male embryos, half of which would be affected. PGT-M could also be used to deselect affected male embryos. While there is a growing list of single-gene defects for which molecular diagnosis is possible, the most common indications include cystic fibrosis, β-thalassemia, muscular dystrophy, Huntington disease, hemophilia, and fragile X disease. It should be noted that when PGT-M is used to deselect affected embryos, the treated couple is not technically infertile but is undergoing an assisted reproductive procedure for the sole purpose of PGT-M. In this setting, PGT-M may be considered an alternative to selective termination of an established pregnancy after diagnosis by amniocentesis or chorionic villus sampling.

**Embryos at a Higher Risk of Translocations**

Balanced translocations occur in 0.2% of the neonatal population but at a higher rate in infertile couples or those with recurrent spontaneous abortions. PGT-SR can be used to deselect embryos carrying the unbalanced translocations members/couples known to carry a chromosomal translocation, thus leading to an increase in fecundity or a decrease in the rate of spontaneous abortion.
Identification of Aneuploid Embryos

Implantation failure of fertilized embryos is common in assisted reproductive procedures; aneuploidy of embryos is thought to contribute to implantation failure and may also be the cause of recurrent spontaneous abortion. The prevalence of aneuploid oocytes increases in older women. These age-related aneuploidies are mainly due to nondisjunction of chromosomes during maternal meiosis. Therefore, PGT-A has been explored as a technique to deselect aneuploid oocytes in older women and is also known as preimplantation genetic testing for aneuploidies. FISH analysis of extruded polar bodies from the oocyte or on blastomeres at day 3 of embryo development was initially used to detect aneuploidy (PGT-A version 1). A limitation of FISH is that analysis is restricted to a number of chromosomes. More recently, newer PGT-A methods have been developed (PGT-A version 2). These methods allow for all chromosomes analysis with genetic platforms including array comparative genomic hybridization and single nucleotide variant chain reaction analysis. Moreover, in addition to older women, PGT-A has been proposed for women with repeated implantation failures and recurrent pregnancy loss (repeat miscarriages).

Summary

For individuals who have an identified elevated risk of a genetic disorder undergoing IVF who receive PGT-M, the evidence includes observational studies and systematic reviews. Relevant outcomes are health status measures and treatment-related morbidity. Data from observational studies and systematic reviews have suggested that PGT-M is associated with the birth of unaffected fetuses when performed for detection of single genetic defects and is associated with a decrease in spontaneous abortions for patients with structural chromosomal abnormalities. Moreover, PGT-M performed for single-gene defects does not appear to be associated with increased risk of obstetric complications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals undergoing IVF, who have no identified elevated risk of a genetic disorder, and are receiving PGT-A, the evidence includes RCTs and meta-analyses. Relevant outcomes are health status measures and treatment-related morbidity. RCTs and meta-analyses of RCTs on initial PGT-A methods (eg, fish in situ hybridization) have found lower or similar ongoing pregnancy and live birth rates compared with IVF without PGT-A. There are fewer RCTs on newer PGT-A methods, and findings are mixed. Meta-analyses of RCTs have found higher implantation rates with PGT-A than with standard care, but improvements in other outcomes are inconsistent. Well-conducted RCTs evaluating PGT-A in the various target populations (eg, women of advanced maternal age, women with recurrent pregnancy loss) are needed before conclusions can be drawn about the impact on the net health benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/2019</td>
<td>Terminology clarified: Preimplantation genetic screening (PGS) changed to preimplantation genetic testing for aneuploidies (PGT-A); Preimplantation genetic diagnosis (PGD) changed to preimplantation genetic testing for monogenic/single gene diseases (PGT-M) and defined coverage criteria for preimplantation genetic testing for structural rearrangements (PGT-SR).</td>
</tr>
<tr>
<td>3/2017</td>
<td>Policy statements clarified.</td>
</tr>
<tr>
<td>10/2016</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>1/2016</td>
<td>Clarified medical necessity criteria.</td>
</tr>
<tr>
<td>11/2015</td>
<td>Clarified medical necessity criteria.</td>
</tr>
<tr>
<td>8/2015</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
<tr>
<td>9/2015</td>
<td>Revised medical necessity language to include IVF for PGT-M and a list of covered diagnoses. Clarified language in investigational statements. Effective 9/1/2015.</td>
</tr>
<tr>
<td>9/2014</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
</tbody>
</table>
Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References